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The importance of hematological parameters in febrile seizures: A case-control study

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Abstract

Aim: Febrile seizures are the most common neurologic disorder of infants and young children. In this study, we aimed to investigate the role of hematological parameters in patients with febrile seizures, which constitute the majority of pediatric emergency department admissions and cause stress in families.

Material and Methods: This is a retrospective, case-control study consisting of a review of charts from a pediatric emergency department of a training and research hospital. Patients were divided into two groups: a study group consisting of 170 children with febrile seizures and a control group of 130 children with fever without seizures. Hematological parameters in peripheral blood samples at the time of the first evaluation were recorded from patients' files and compared between the two groups.

Results: The major findings of the study were that neutrophil count was higher, lymphocyte count was lower, neutrophil-to-lymphocyte ratio was higher and hematocrit, mean corpuscular volume, mean platelet volume and platelet count were lower in children with febrile seizures.

Discussion: Febrile seizures are common in children under 5 years of age and constitute the majority of pediatric emergency admissions. In this study, we found that neutrophil count and platelet count were the most important protective factors associated with febrile seizures and we think that they may be reliable, easily accessible and inexpensive markers for determining the risk of febrile seizures.

Keywords

Febrile Seizure, Neutrophil Count, Neutrophil-To-Lymphocyte Ratio, Platelet Count

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Introduction

Febrile seizures (FSs) are the most common neurologic disorder of infants and young children. These seizures occur with fever without a defined cause such as central nervous system infection or metabolic disorder in children aged 6 months to 5 years and without a previous history of afebrile seizure [1]. In studies conducted in the United States and Europe, the frequency of FS has been reported as 2-4%, while in Japan, it was found to be 9-10% [2,3]. FS can be classified into two groups: complex FS lasts ≥15 min, is focal, and recurs within 24 hours, while simple FS lasts <15 min, occurs only once in 24 hours and is generalized [4]. While simple FSs are benign and self-limiting with no risk of immediate recurrence, complex FSs entail a higher risk of recurrent FSs and a slightly higher risk of future non-febrile seizures [5].

The pathophysiology of FS is not clear. Genetic and environmental factors are thought to be effective together. Identified risk factors are fever, infections, vaccination, and genetic inheritance [6]. Most FSs are seen when fever first appears or starts to rise. Fever is a very common symptom in childhood, but why it causes FSs in some children has not yet been explained. However, recent studies suggest that inflammation causing fever response may also play a role in the pathogenesis of FSs [7]. The link between inflammation and FSs has been explored in recent years [8]. Among the pro-inflammatory cytokines, interleukin 1-beta (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α) were found to be significantly higher in children with FSs. Anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA) and IL-10 have a negative effect on inflammation. However, in susceptible patients, it seems that the anti-inflammatory effect is lost and the systemic pro-inflammatory cytokine levels increase, which leads to FSs [7,8]. The major problem with these types of cytokines is that they are expensive and difficult to obtain and to determine their blood levels. Therefore, inexpensive and easily accessible biomarkers are needed. Complete blood count is a simple and inexpensive test that it is available in all hospitals. At present, several new parameters reflecting inflammatory indices, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red blood cell distribution width (RDW), mean platelet volume (MPV), platelet count and mean platelet volume/platelet count ratio (MPR) has begun to be investigated in inflammation-related diseases [9]. Moreover, the predictive value of these biomarkers has become a new focus of clinical research in patients with FSs and it has started to attract attention due to its low cost [10-12].

In this study, we aimed to investigate the role of hematological parameters in patients with FSs, which constitute the majority of pediatric emergency department admissions and cause stress in families.

Material and Methods

Study Design

This is a retrospective, case-control study consisting of a review of charts from a pediatric emergency department of a training and research hospital. The study presents an analysis of 300 children aged 6 months to 5 years who were admitted to the pediatric emergency department because of FSs or fever without seizures between February 2019 and December 2020. Patients were divided into two groups: the study group consisting of 170 children with FSs and a control group of 130 children with fever without seizures. Simple FS was defined as a single seizure that lasted less than 15 minutes, occurred once in a 24-hour period, and had no focal features. Complex FS was defined as episodes that lasted more than 15 minutes, occurred more than once in 24 hours, or had focal features [4]. Patients with a previous history of FS were considered to have recurrent FSs. Children aged between 6 months and 5 years who presented to the pediatric emergency department with high fever but did not have seizures were included in the control group. Exclusion criteria were applied for cases of FS for children who had known central nervous system abnormalities, history of afebrile seizures, previous evidence of intracranial infection, cases with chronic diseases or continuous medication use and for all patients without laboratory results. The study was approved by the İzmir Bakırçay University Ethics Committee (Decision No.: 212 Research No.: 194 Date: 04.03.2021) and followed the guidelines of the Declaration of Helsinki for research involving human subjects.

Laboratory Analysis

White blood cell count (WBC), red blood cell count (RBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), red blood cell distribution width (RDW), mean platelet volume (MPV), platelet count (PLT), MPV/PLT ratio (MPR), numbers of neutrophils and lymphocytes, neutrophil-to-lymphocyte ratio (NLR) and PLT/ lymphocyte ratio (PLR) in peripheral blood samples at the time of the first evaluation were recorded from patients' files. NLR was calculated by dividing the obtained numbers of neutrophils and lymphocytes. MPR was calculated by dividing the MPV by the platelet count. PLR was calculated by dividing the obtained numbers of platelets and lymphocytes.

Statistical Analysis

Categorical variables were descriptively presented as counts and percentages. Continuous variables were presented as mean and standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. The chi-square or Fisher exact test was used to compare categorical data as appropriate. The Student t-test was used to compare the parametric data of two groups and the Mann-Whitney U test was used to compare the non-parametric data of two independent groups. Receiver operating characteristic (ROC) curve analysis was used for calculating the optimal cut-off values, sensitivity, and specificity of NLR. Linear regression analysis and binary logistic analysis were used to study the association between the FSs (dependent variable) and the detection factors (independent variables). The

analyses were performed with SPSS 24.0 for Mac (IBM Corp., Armonk, NY, USA). Values of $p<0.05$ were considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 300 patients, including 170 patients with FSs and 130 patients with fever without seizures, were included in the

study. Seventeen (10%) patients with FSs were evaluated as complex FS. 51.2% (n:87) of the FS group were male, 48.8% (n:83) were female, and the mean age was 23.4±11.3 months. In the control group, 64 (49.2%) were male, 66 (50.8%) were female, and the mean age was 20.9±14.6 months. There was no statistically significant difference between the two groups in terms of age and gender. When the FS group was examined, it was seen that 103 patients had first and 67 (%39) patients had recurrent FSs.

Table 1. Comparison of hematological parameters of children with febrile seizures and control group

		Febrile Seizures (n: 170)	Control group (n: 130)	p value
Age (month), Mean±SD		23,4±11,3	20,9±14,6	0,1
Gender (n, %)	Male	87 (51,2)	64 (49,2)	0,26
	Female	83 (48,8)	66 (50,8)	
WBC (×10³/mm³) Median (IQR)		11,1 (8,1-14,8)	10,5 (8,1-14,4)	0,43
Neutrophil count (×10³/mm³) Median (IQR)		6,7 (4,4-9,8)	4,7 (3,2-8,1)	p<0.001
Lymphocyte count (×10³/mm³) Median (IQR)		2,9 (2,0-4,1)	3,3 (1,9-5,5)	0,02
Hb (g/dL), Median (IQR)		11,4 (10,8-12,2)	11,6 (10,8-12,3)	0,24
Hct, Median (IQR)		33,8 (31,6-35,6)	34,5 (32,1-36,2)	0,04
RBC (106/uL), Median (IQR)		4,5 (4,3-4,8)	4,6 (4,3-4,7)	0,56
MCHC (g/dL), Median (IQR)		34 (33,5-34,5)	33,9 (33,3-34,4)	0,08
MCH (pg), Median (IQR)		25,6 (24,0-26,6)	25,9 (23,9-27,0)	0,18
MCV (fL), Median (IQR)		75 (71,3-77,8)	76,2 (71,9-78,9)	0,04
RDW (%), Median (IQR)		14,1 (13,2-15,6)	14 (13,1-15,5)	0,73
MPV(fL), Median (IQR)		7,1 (6,7-7,5)	7,4 (6,8-7,8)	0,01
PDW (%), Median (IQR)		16,4 (16,1-16,8)	16,4 (16,1-16,8)	0,78
PLT (×109/L), Median (IQR)		293,5 (226,7-377,2)	336,5 (263,7-410,5)	0,001
NLR, Median (IQR)		2,4 (1,4-3,9)	1,4 (0,66-3,2)	p<0.001
MPR, Median (IQR)		0,023 (0,017-0,03)	0,022 (0,017-0,028)	0,28
PLR, Median (IQR)		95,4 (73,9-155,4)	95 (65,5-168,9)	0,84

Table 2. Logistic Analysis of Risk Factors for Febrile Seizure

Variable	Regression Coefficient	Standard Error	p value	OR	95% CI
Neutrophil count	-0,253	0,054	<0,001	0,776	0,698-0,863
Platelet count	0,007	0,002	<0,001	1,007	1,004-1,010

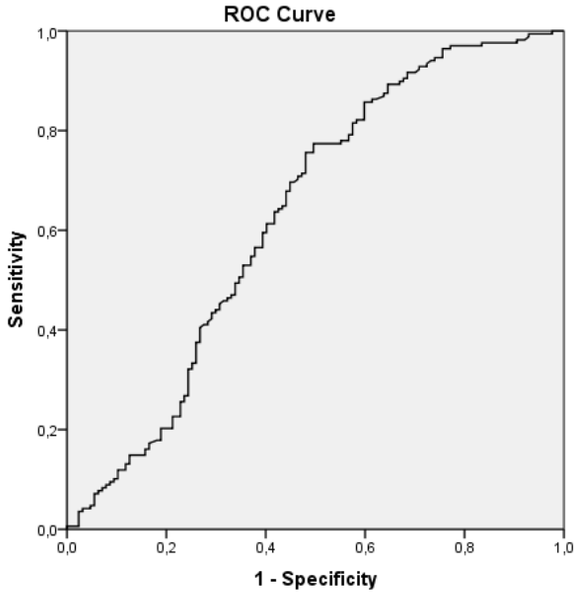

Figure 1. Receiver operating characteristic curve analyses of neutrophil-to-lymphocyte ratio for predicting febrile seizure in children with fever

Hematological parameters of patients with FSs and those with fever without seizure were compared. The neutrophil count was higher, the lymphocyte count was lower, and the NLR was higher in the FS group compared to the control group, and a statistically significant difference was found (p<0.001, p=0.02, p<0.001). HCT and MCV levels were found to be statistically significantly lower in the FS group (p=0.04, p=0.04). When platelet parameters were examined, it was found that MPV and PLT count were statistically significantly lower in the FS group (p=0.01, p=0.001). No significant difference was found in MPR and PLR (p>0.05). The laboratory parameters of the patients are shown in Table 1. ROC analysis was performed and the value of the area under the curve (AUC) for NLR in cases of FS was found to be 0.631 (95% confidence interval [CI]: 0.564-0.698, p<0.001) (Figure 1). At a cut-off point of 1.72, the sensitivity and specificity of NLR for FS were 64.9% and 44.1%, respectively. Linear regression analysis showed that neutrophil count, lymphocyte count, NLR, HCT, MPV and PLT count were closely linked to FSs. Subsequent binary logistic analysis revealed that neutrophil count and PLT count were the most important protective factors associated with FSs in children included in this study (odds ratio [OR] = 0.776; 95% confidence interval [CI]: 0.698-0.863; p<0.001, OR=1.007, 95% CI=1.004-1.010 P<0.001) (Table 2).

When hematological parameters were compared between patients with simple and complex FSs, and patients with first and recurrent FSs, no significant difference was found (p>0.05).

Discussion

In the present study, we have analyzed the hematological parameters of children presenting with FSs and children with fever without seizures who were admitted to a pediatric emergency department. The major findings of the study were that neutrophil count was higher, lymphocyte count was lower, NLR was higher and HCT, MCV, MPV and PLT counts were lower in children with FSs.

In this study, the mean age of the children with FSs was approximately 2 years old and most of them were male. Sharawat et al. found that most of the children with FSs were male and younger than 2 years of age [13]. In a similar study conducted in Poland, the mean age of children with FSs was 23 months and 61.9% were male [10]. These sex and age distributions show that FSs are more common in younger age groups and in boys, as confirmed by pediatric textbooks [6].

In the present study, the neutrophil count was significantly higher and the lymphocyte count was lower in the group of children with FSs compared to children with fever without seizures. In a study conducted by Teran et al. with 219 children with FSs, they found leukocytosis in 24% of cases and neutrophilia in 91% [20]. Similarly, Romanowska et al. found that neutrophil counts were higher in the FS group [14]. High neutrophil counts may be due to muscle contractions during seizures, inflammatory reaction, or toxins circulating in the blood [15]. This result may

also represent a simple response to the release of steroids and endorphins known to occur after an episode of a seizure [16]. Children with FSs had significantly higher NLRs in comparison to children with fever without seizures in our study. Liu et al. assessed selected laboratory results in febrile children with and without seizures in China and they found that the mean NLR was significantly higher in the FS group compared to the control group. The best NLR cut-off value was ≥1.13 [11]. In the present study, we found that the best cut-off value for NLR was 1.72. Tang and Chen found in their study in hospitalized patients with FSs that NLR was higher in patients with FSs than in the healthy control group [17]. Goksugur et al. found that NLR in patients with complex FSs was significantly higher than that in patients with simple FSs [18]. Yigit et al. concluded that NLR and the percentage of neutrophils were significantly lower in the simple seizure group compared to the complex seizure group (19). NLR, which is calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes, is an inflammation index and may serve as an emerging parameter that reflects systemic inflammation in various diseases [9,20]. Neutrophils are the most important cells of the immune system. They are the first cells to migrate into the area of injury and can induce the secretion of several inflammatory cytokines associated with FSs; IL-1β, IL-6 and TNF-α play especially important roles in pathogenesis [8]. Lymphocytes have been shown to secrete IL-10, a multifunctional anti-inflammatory cytokine, suggesting that lymphocyte function is associated with resistance to FSs [7,8]. NLR is an objective, reproducible, low-cost, and available indicator of inflammation that indicates the balance between lymphocytes and neutrophils. Although the mechanism underlying the association is complex, it may be related to increased neutrophil-dependent inflammation and reduced lymphocyte mediated anti-inflammation response [7,8]. Thus, it is not surprising that elevated NLR levels are associated with increased risk of FSs.

In this study, we found that MCV and HCT in the FS group were significantly lower than in the control group. Iron deficiency anemia influences cell-mediated, humoral, and nonspecific immunity and it has been shown that the prevalence of iron deficiency anemia is higher among children with FS compared with healthy controls. Iron deficiency can reduce the metabolism of some neurotransmitters, which may alter the epilepsy threshold in children [21].

In this study, we found that PLT counts and MPV were significantly lower in the FSs group than in the control group. According to research conducted by Liu et al, the MPV in the FS group was higher and the PLT count was lower than that in the control group [11]. Tang and Chen found that PLT count and MPV were significantly lower in patients with FSs than in the healthy control group [17]. A few studies have reviewed the relationship between MPV and FSs with inconsistent results. Therefore, the results obtained may differ from each other. Although the underlying mechanisms are still to be elucidated, some hypotheses can be proposed. Causes of platelet activation are systemic inflammation, oxidative stress and hypoxemia and these factors may coexist during a FS. Triggering platelet aggregation leads to the release of many chemical mediators and endothelial damage, resulting in the release of inflammatory cytokines such as IL-1 and IL-6. These reactions can lead to the depletion of more platelets or to macrophages phagosizing more platelets, resulting in a decrease in PLT count in the peripheral blood [22,23]. MPV reflects the size of platelets and the generation rate of platelets in bone marrow and is one of the indicators of platelet activation [24]. MPV and PLT count are two major indicators for evaluating platelet activation and severity of inflammation [22-24]. Therefore, it is considered that the risk of FS may be related to platelet activation and PLT count and MPV have been closely linked to the pathogenesis of FS [11,17]. Our findings demonstrated that PLT count and MPV may be reliable markers for FS risk.

Limitations

There are some limitations to our study. First, the study was conducted in a single center and retrospectively. Second, the sample size, and especially that of children with complex FSs, was small. The low number of complex FS cases prevented us from revealing any differences between simple and complex FSs.

Conclusion

FSs are common in children under 5 years of age and constitute the majority of pediatric emergency admissions. This is also very important as FSs cause fear and stress for the parents of these children. In this study, we found that the neutrophil count and the platelet count were the most important protective factors associated with FSs and we think that they may be reliable, easily accessible and inexpensive markers for determining the risk of FSs. The pathophysiology of FSs is not clear and further studies with large case series are needed to clarify this.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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